REMARKS

Applicants respectfully request reconsideration and withdrawal of the final rejection, in view of the following facts and arguments, which are viewed to place this application in condition for allowance or in better form for consideration on appeal, as permitted by Rule 1.116(b).

Claims 1-17 remain pending in the application, with claims 1, 8 and 9 being independent. No claim amendments are requested.

Applicants requests favorable reconsideration and withdrawal of the rejections set forth in the above-noted Final Office Action.

The rejection of claims 1-17 technically under 35 U.S.C. §112, first paragraph, as lacking enablement, is again respectfully traversed. The Examiner again has acknowledged earlier that the specification does reasonably demonstrate efficacy as to a composition consisting essentially of chlorogenic acid and 3-o-p-coumaryl quinic acid. Yet, the Examiner then inquires as to any working examples or data concerning a pharmaceutical composition consisting essentially of chlorogenic acid and broadly " p-coumaryl quinic acid"

At page 14 of the Final Office Action, the exact question is posed as "the Examiner has not questioned the enablement of the composition but as stated on page 3 of the office action the rejection is based on enablement for a pharmaceutical compositions consisting essentially of chlorogenic acid and p-coumaryl quinic acid." Applicants respond again that the distinctly claimed invention more narrowly relates to a pharmaceutically effective amount of chlorogenic acid and 3-o-p-coumaryl quinic acid isolated from any plant parts of *Piper betel* or any other

source, optionally along with pharmaceutically acceptable additives. Therefore, on the record of this case, Applicants' invention as distinctly claimed is fully enabled under 35 U.S.C. §112, first paragraph.

As further discussed by the Examiner in the § 112 rejection, P-coumaryl quinic acid exists as 3-o-p-coumaryl quinic acid, 4-o-p-coumaryl quinic acid and 5-o-p-coumaryl quinic acid. The Examiner states on page 5 of the Office Action, "Thus, given such differences in the molecular structure of such p-coumaryl quinic acids and in the absence of showing that the structural disparity between any and all p-coumaryl quinic acids exhibit the same functional effect for inhibition of growth leukemic cell lines of cell type K562 it is not reasonable to predict that a claim-designated composition comprising any and all p-coumaryl quinic acids would provide the same beneficial functional effect for the treatment of acute and chromic myeloid leukemia in animals and humans." That is the point.

Attached is a Supplemental Information Disclosure Statement to make of record two publications that tend to corroborate why it is generally recognized that unexpected results will occur. For example, it has been observed that catechins, epicatechin gallate, epigallocatechin gallate, which are constituents of tea extract, can show antimutagenic activity on cultured chinese hamster cells (Kuroda Y. Mutat. Res. 361,179-86, 1996). In addition, epigallocatechin gallate , one of the main constituents of tea extract, has been observed to have anticarcinogenic activity (Komori A. et. al. JPN J. Clin. Oncol. 23, 186-90,1993). Therefore, while Tea Extract / Plant Extract containing a mixture of Polyphenols including Chlorogenic Acid (CA) and Quinic Acid may have been shown to have anti-mutagenic and anti-carcinogenic activities, the prior art has

not recognized anti- chronic myeloid leukemia (CML) and anti- acute myeloid leukemia(AML) activity by Chlorogenic Acid and/or Quinic Acid. The anti-mutagenic and anti-carcinogenic activities of the extracts discussed in these references could have been mediated by other polyphenols present in the extract. The present patent application shows anti-CML and anti-AML activity of defined ratios of defined molecules i.e. Chlorogenic Acid (CA) and 3-o-p-coumaryl quinic acid (PCQ). Therefore, while p-coumaryl quinic acid may exist as 3-o-p-coumaryl quinic acid, 4-o-p- coumaryl quinic acid and 5-o-p- coumaryl quinic acid, it appears that the difference in each molecular structure may well be responsible for differing effects. In the present application, only 3-o-p-coumaryl quinic acid has been identified to have the specified effects.

The present application particularly points out and then distinctly claims only 3-o-p-coumaryl quinic acid, as being detected in *Piper betel*. Further, 3-o-p-coumaryl quinic acid was exampled as being effective for treatment of acute and chronic myeloid leukemia and lymphoid leukemia, and then only 3-o-p-coumaryl quinic acid was distinctly recited within Claims 1-17. Claims 1-17 are not directed toward a pharmaceutical composition consisting essentially of chlorogenic acid and any and all possible forms of p-coumaryl quinic acids. The Examiner's § 112 rejection, therefore, is moot when a claimed composition consists essentially of chlorogenic acid and 3-o-p-coumaryl quinic acid. Reconsideration and withdrawal of the § 112 rejection is respectfully requested.

Claims 1-17 were rejected substantively under 35 U.S.C. § 103(a) as being unpatentable over Kuroda et al. (Mutation Research/Reviews in Mutation Research, Volume 436, Issue 1,

January 1999, Pages 69-97) in view of Yang et al. (Drug Metabolism Reviews, Volume 33, Issues 3 & 4, December 2001, Pages 237-253). Claims 1-17 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Ferguson (Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, Volume 475, Issues 1 & 2, April 18, 2001, Pages 89-111). Claims 1-17 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang et al. (Drug Metabolism Reviews, Volume 33, Issues 3& 4, December 2001, Pages 237-253). Applicants submit that the cited art, whether taken individually or in combination, does not teach or suggest many features of the present invention, as previously recited in these claims. Therefore, these rejections are respectfully traversed.

In one aspect of the present invention, independent claim 1 recites a method of treating acute and chronic myeloid leukemia (AML & CML) and lymphoid leukemia, in a mammal, in order to obtain a percentage growth inhibition of at least one of promonocyte cells, Erythroleukemia cells, or CML's leukemic cells. The method comprises administering a pharmaceutical composition that is a synergistic combination consisting essentially of a pharmaceutically effective amount of chlorogenic acid (CA) and 3-o-p-Coumaryl quinic acid (PCQ) isolated from any plant parts of *Piper betel* or any other source, optionally along with pharmaceutically acceptable additives.

In another aspect of the present invention, independent claim 8 recites a method, of treating AML & CML and lymphoid leukemia, in a mammal, in order to obtain a percentage growth inhibition of at least one of promonocyte cells, Erythroleukemia cells, or CML's leukemic cells. The method comprises administering a pharmaceutical composition, consisting

essentially of a pharmaceutically effective amount of CA isolated from any plant parts of *Piper betel* or any other source, optionally along with pharmaceutically acceptable additives wherein the percentage growth inhibition of Erythroleukemia cells is up to about 30% with CA.

In a further aspect of the present invention, independent claim 9 recites a method of treating AML & CML and lymphoid leukemia, in a mammal, in order to obtain a percentage growth inhibition of at least one of promonocyte cells, Erythroleukemia cells, or CML's leukemic cells. The method comprises administering a pharmaceutical composition, consisting essentially of a pharmaceutically effective amount of PCQ isolated from any plant parts of *Piper betel* or any other source, optionally along with pharmaceutically acceptable additives, wherein the percentage growth inhibition of Erythroleukemia cells is up to about 8% with PCQ.

Applicants submit that the cited art, whether taken individually or in combination, does not teach or suggest such features of Applicants' present invention, as recited in independent claims 1, 8 and 9.

The Examiner considers Kuroda et al. to teach an antimutagenic activity against various mutagens of tea extracts of green and black teas and polyphenols including ECG and EGCG, demonstrated in microbial systems *Salmonella typhimurium* and *Escherichia coli*, mammalian cell systems and *in vivo* animal tests. The Examiner further considers Kuroda et al. to teach that the anticarcinogenic activity of tea phenols has been shown in experimental animals such as rats and mice, presenting with a leukemia.

The Examiner is thanked for noting, however, that Kuroda et al. fails to teach the polyphenols of the black and green teas, a particular CA and PCQ, mode of administration, dose

levels administered, and a percentage growth inhibition as recited in independent claims 1, 8, and 9. It is the Examiners position, however, that Yang et al. meets the deficiencies of Kuroda et al., by teaching the polyphenols of black and green teas as inclusive of CA and quinic acid, which is useful in prevention of carcinogenesis, therefore rendering Applicants' invention obvious.

The Examiner views the Ferguson publication to teach a green tea extract that comprises polyphenols such as epigallocatechin gallate, chlorogenic acid and coumarylquinic acid.

The Examiner is thanked for noting, however, that Ferguson fails to teach the method of treating acute and chronic leukemia and lymphoid leukemia, the additives, the amount of CA and PCQ, the mode of administration, dose levels administered, or the percentage growth inhibition claimed. Applicants add that in addition to the numerous deficiencies of Ferguson noted by the Examiner, Ferguson merely discloses coumarylquinic acid and not 3-o-p Coumaryl quinic acid.

Tea Extract and Plant Extract containing a mixture of Polyphenols including Chlorogenic Acid and Quinic Acid may have some anti-mutagenic and anti-carcinogenic activities, as specified in Kuroda et al., Yang et al., and Ferguson. None of these documents, however, in any way teach or suggest a anti-chronic myeloid leukemia and anti-acute myeloid leukemia activity by Chlorogenic Acid and/or Quinic Acid. The anti-mutagenic and anti-carcinogenic activities of the extracts reported in Kuroda et al., Yang et al., and Ferguson could be mediated by other polyphenols present in the extract.

In contrast, only the present application teaches anti-chronic myeloid leukemia and anti-acute myeloid leukemia activity through defined ratios of defined molecules, *i.e.* Chlorogenic Acid and 3-o-p-coumaryl quinic acid. Kuroda et al., Yang et al., and Ferguson, therefore, fail to

teach or suggest the specific invention as limited in independent claims 1, 8 and 9.

Applicants further submit that it would not have been obvious to one skilled in the art to use either 4-coumaryl quinic acid or coumaryl quinic acid as disclosed in Yang et al. and Ferguson respectively, instead of 3-o-p-coumaryl quinic acid, for the treatment of acute and chronic myeloid leukemia and lymphoid leukemia in mammals. P-coumaryl quinic acid exists as 3-o-p-coumaryl quinic acid, 4-o-p-coumaryl quinic acid and 5-o-p-coumaryl quinic acid. The difference in the molecular structures appear to dictate different effects.

Only the present application teaches that 3-o-p-coumaryl quinic acid uniquely has been shown effective for the treatment of acute and chronic myeloid leukemia and lymphoid leukemia. Applicants submit, therefore, that it would not have been obvious to one skilled in the art to use either 4-coumaryl quinic acid or coumaryl quinic acid for the treatment of acute and chronic myeloid leukemia and lymphoid leukemia in mammals.

For the foregoing reasons, Applicants submit that the present invention, as recited in independent claims 1, 8 and 9, is patentably defined over the cited art, whether that art is taken individually or in combination.

Dependent claims 2-7 and 10-17 also should be deemed allowable, in their own right, for defining other patentable features of the present invention in addition to those recited in their respective independent claims. Further individual consideration of these dependent claims is requested.

Applicants submit that the instant application is in condition for allowance. Applicants, therefore, also requests favorable reconsideration, withdrawal of the rejection set forth in the

above-noted Office Action, and an early Notice of Allowance.

Any additional fee required to render this response timely may be charged to Deposit Acct. No. 06-1205. All correspondence should continue to be directed to the below-listed address.

The undersigned attorney of record may be reached in Washington, DC by telephone at (202) 530-1010.

Respectfully submitted,

/warreneolsen/
Warren E. Olsen (Reg. No. 27,290)

FITZPATRICK, CELLA, HARPER & SCINTO
Customer No.: 05514
30 Rockefeller Plaza
New York, New York 10112-3800
Facsimile: (212) 218-2200